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(71) Applicant *(for all designated States except US)*: MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: RUPNIAK, Nadia, Melanie [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(74) Agent: HISCOCK, Ian, James; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

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(54) Title: USE OF AN NK-1 RECEPTOR ANTAGONIST FOR TREATING COGNITIVE DISORDERS

(57) Abstract

The present invention provides the use of an NK-1 receptor antagonist for the manufacture of a medicament adapted for oral administration for the treatment or prevention of cognitive disorders, methods of medical treatment using such an NK-1 receptor antagonist and pharmaceutical compositions comprising it.

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USE OF A NK-1 RECEPTOR ANTAGONIST FOR TREATING COGNITIVE DISORDERS

This invention relates to the treatment or prevention of certain cognitive disorders by the administration of a NK-1 receptor antagonist, in particular, 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified. The prominent disturbance associated with these conditions is a clinically significant deficit in cognition or memory that represents a significant change from a previous level of functioning.

For instance, dementia is now defined as a syndrome consisting of progressive impairment in two or more areas of cognition (i.e. memory, language, visuospatial and perceptual ability, thinking and problem solving, and personality) sufficient to interfere with work, social function or relationships.

An amnestic disorder is characterised by memory impairment in the absence of other significant cognitive impairments.

Pharmacological treatment of such cognitive disorders is poorly developed. In some instances, antidepressants, hypnotics or antipsychotics may be used in order to manage specific behavioural disturbances associated with the cognitive disorder. Such treatments, however, may be compromised by the side effects associated with these classes of pharmacological agent and, as such, are far from ideal means for treating cognitive disorders.

Neurokinin 1 (NK-1; substance P) receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinins, and in particular substance P. Examples of conditions in which substance P has been

implicated include disorders of the central nervous system such as anxiety, depression and psychosis (see, for instance, International (PCT) patent specification Nos. WO 95/16679, WO 95/18124 and WO 95/23798).

More recently, International (PCT) patent specification No. WO 96/24353 (published 15th August 1996) suggests that a more efficacious and safe treatment of psychiatric disorders would be achieved using a combination of a tachykinin antagonist and a serotonin agonist or selective serotonin reuptake inhibitor (SSRI). However, such as regimen would not be free of side-effects due to the serotonin agonist or SSRI.

In view of the short-comings of existing therapy, there is a need for new, safe and effective treatment for cognitive disorders.

The present invention provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof in an oral, once-a-day medicament for the treatment of cognitive disorders. The compounds of this class advantageously exhibit a rapid onset of action and a reduced side-effect profile when compared against conventional antidepressant or antipsychotic agents.

The exceptional pharmacology of the NK-1 receptor antagonist of use in the present invention enables the treatment of cognitive disorders, without the need for concomitant therapy using tricyclic antidepressants or monoamine oxidase inhibitors, or antipsychotic agents, or in particular, without the need for concomitant use of a serotonin agonist or an SSRI.

Furthermore, the exceptional pharmacology of the NK-1 receptor antagonist of use in the present invention results in a rapid onset of action.

The present invention accordingly provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament adapted for oral administration for the treatment or prevention of cognitive disorders.

The present invention also provides a method for the treatment or prevention of cognitive disorders, which method comprises the oral administration to a patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present invention, there is provided an oral pharmaceutical composition for the treatment of cognitive disorders which comprises 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

There exists a patient population in whom cognitive disorders are inadequately treated with existing antidepressant therapy. Furthermore, some patients may be adversely affected by the side-effects of existing antidepressant drugs.

The present invention accordingly provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament adapted for oral administration for the treatment or prevention of cognitive disorders in a patient who is non-responsive to heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, serotonin agonists or antagonists, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, serotonin agonists or antagonists, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated.

The present invention also provides a method for the treatment or prevention of cognitive disorders in a patient who is non-responsive to heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs,

serotonin agonists or antagonists, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, serotonin agonists or antagonists, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

Furthermore, there exists a patient population in whom cognitive disorders are inadequately treated with existing antipsychotic therapy. Furthermore, some patients may be adversely affected by the side-effects of antipsychotic drugs.

The present invention accordingly provides the use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament adapted for oral administration for the treatment or prevention of cognitive disorders in a patient who is non-responsive to antipsychotic agents, or for whom antipsychotic agents are contraindicated.

The present invention also provides a method for the treatment or prevention of cognitive disorders in the patient who is non-responsive to antipsychotic agents, or for whom antipsychotic agents are contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

As used herein, the term "cognitive disorders" includes dementia, amnestic disorders and cognitive disorders not otherwise specified.

In particular, the term "cognitive disorders" includes dementia caused by degenerative disorders, lesions, trauma, infections, vascular disorders, toxins, anoxia, vitamin deficiency and endocrine disorders. Specific examples of these causes include degenerative disorders such as Alzheimer's disease, multiple sclerosis, Parkinson's disease, normal pressure hydrocephalus and Huntington's chorea; space occupying lesions including tumors and chronic subdural haematoma; trauma including severe head injury; infections including postencephalitis and syphilis; vascular disorders including multi-infarct dementia; toxins including alcohol; anoxia caused by cardiac arrest and carbon monoxide poisoning, vitamin deficiencies including lack of vitamin B_{12}; and endocrine disorders including hypothyroidism.

Furthermore, the term "cognitive disorders" includes amnestic disorders caused by alcohol (Korsakoff psychosis) and other causes of thiamine deficiency; bilateral temporal lobe damage due to herpes simplex encephalitis and other limbic encephalitis, neuronal loss secondary to anoxia/hypoglycaemia/severe convulsions, and surgery; degenerative disorders including Alzheimer's and Pick's diseases; vascular disorders including bilateral infarction, hippocampal infarction and bilateral cingulate cortex infarction; and pathology around ventricle III including tumors, chronic meningitis and neurosarcoidosis.

Also, as used herein, the term "cognitive disorders" includes cognitive impairment resulting from other medical conditions, most especially resulting from depression and/or anxiety.

As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the aforementioned conditions.

In particular, the NK-1 receptor antagonist of use in the present invention is the compound 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

Full descriptions of the preparation of the NK-1 receptor antagonist which may be employed in the present invention may be found in International Patent Specification No. WO 95/18124 and US Patent No. 5,612,337.

Suitable pharmaceutically acceptable salts of the NK-1 receptor antagonist of use in the present invention include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group.

Preferably the compositions containing the NK-1 receptor antagonist of use according to the present invention are in unit dosage forms such as tablets, pills, capsules, wafers and the like. Additionally, the NK-1 receptor antagonist of use according to the present invention may be presented as granules or powders for extemporaneous formulation as volume defined solutions or suspensions. Alternatively, the NK-1 receptor antagonist of use according to the present invention may be presented in ready-prepared volume defined solutions or suspensions. Preferred forms are tablets and capsules.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the

composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil or soybean oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions of the present invention may also be administered via the buccal cavity using conventional technology, for example, absorption wafers.

Compositions in the form of tablets, pills, capsules or wafers for oral administration are particularly preferred.

A minimum dosage level for the NK-1 receptor antagonist is about 1mg per day, preferably about 5mg per day and especially about 10mg per

day. A maximum dosage level for the NK-1 receptor antagonist is about 1500mg per day, preferably about 1000mg per day and especially about 500mg per day. The compounds are administered once a day.

It will be appreciated that the amount of the NK-1 receptor antagonist required for use in the treatment or prevention of cognitive disorders will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the patient's physician or pharmacist.

The activity of the NK-1 receptor antagonist of use in the present invention may be measured using the following assays:

ASSAY 1: NK-1 Receptor binding

NK-1 receptor binding assays are performed in intact Chinese hamster ovary (CHO) cells expressing the human NK-1 receptor using a modification of the assay conditions described by Cascieri *et al*, *J. Pharmacol. Exp. Ther.*, 1992, 42, 458. Typically the receptor is expressed at a level of $3x10^5$ receptors per cell. Cells are grown in monolayer culture, detached from the plate with enzyme-free dissociation solution (Speciality Media Inc.), and washed prior to use in the assay. ^{125}I-Tyr^8-substance P (0.1nM, 2000Ci/mmol; New England Nuclear) is incubated in the presence or absence of test compounds (dissolved in 5µl dimethylsulphoxide, DMSO) with $5x10^4$ CHO cells. Ligand binding is performed in 0.25ml of 50mM Tris-HCl, pH7.5, containing 5mM $MnCl_2$, 150mM NaCl, 0.02% bovine serum albumin (Sigma), 50µg/ml chymostatin (Peninsula), 0.1nM phenylmethylsulphonyl fluoride, 2µg/ml pepstatin, 2µg/ml leupeptin and 2.8µg/ml furoyl saccharine. The incubation proceeds at room temperature until equilibrium is achieved (>40 minutes) and the receptor-ligand complex is harvested by filtration over GF/C filters pre-soaked in 0.1% polyethylenimine using a Tomtek 96-well harvester. Non-

specific binding is determined using excess substance P (1μM) and represents <10% of total binding.

ASSAY 2: Gerbil Foot-Tapping

CNS-penetrant NK-1 receptor antagonists for use in the present invention can be identified by their ability to inhibit foot tapping in gerbils induced by anxiogenic agents (such as pentagastrin) or central infusion of NK-1 receptor agonists such as GR73632, or caused by aversive stimulation such as foot shock or single housing, based on the method of Rupniak & Williams, *Eur. J. Pharmacol.*, 1994, **265**, 179.

Male or female Mongolian gerbils (35-70g) are anaesthetised by inhalation of an isoflurane/oxygen mixture to permit exposure of the jugular vein in order to permit administration of test compounds or vehicle in an injection volume of 5ml/kg i.v. Alternatively, test compounds may be administered orally or by subcutaneous or intraperitoneal routes. A skin incision is then made in the midline of the scalp to expose the skull. An anxiogenic agent (e.g. pentagastrin) or a selective NK-1 receptor agonist (e.g. GR73632 (d Ala[L-Pro^9,Me-Leu^{10}]-substance P-(7-11)) is infused directly into the cerebral ventricles (e.g. 3pmol in 5μl i.c.v., depending on test substance) by vertical insertion of a cuffed 27 gauge needle to a depth of 4.5mm below bregma. The scalp incision is closed and the animal allowed to recover from anaesthesia in a clear perspex observation box (25cm x 20cm x 20cm). The duration and/or intensity of hind foot tapping is then recorded continuously for approximately 5 minutes. Alternatively, the ability of test compounds to inhibit foot tapping evoked by aversive stimulation, such as foot shock or single housing, may be studied using a similar method of quantification.

ASSAY 3: Ferret Emesis

Individually housed male ferrets (1.0 -2.5 kg) are dosed orally by gavage with test compound. Ten minutes later they are fed with

approximately 100g of tinned cat food. At 60 minutes following oral dosing, cisplatin (10mg/kg) is given i.v. *via* a jugular vein catheter inserted under a brief period of halothane anaesthesia. The catheter is then removed, the jugular vein ligated and the skin incision closed. The ferrets recover rapidly from the anaesthetic and are mobile within 10-20 minutes. The animals are observed continuously during recovery from the anaesthetic and for 4 hours following the cisplatin injection, after which time the animals are killed humanely. The numbers of retches and vomits occurring during the 4 hours after cisplatin administration are recorded by trained observers.

ASSAY 4: Separation-Induced Vocalisation

Male and female guinea-pigs pups are housed in family groups with their mothers and littermates throughout the study. Experiments are commenced after weaning when the pups are 2 weeks old. Before entering an experiment, the pups are screened to ensure that a vigorous vocalisation response is reproducibly elicited following maternal separation. The pups are placed individually in an observation cage (55cm x 39cm x 19cm) in a room physically isolated from the home cage for 15 minutes and the duration of vocalisation during this baseline period is recorded. Only animals which vocalise for longer than 5 minutes are employed for drug challenge studies (approximately 50% of available pups may fail to reach this criterion). On test days each pup receives an oral dose or an s.c. or i.p. injection of test compound or vehicle and is then immediately returned to the home cage with its mother and siblings for 30 to 60 minutes (or for up to 4 hours following an oral dose, dependant upon the oral pharmacokinetics of the test compound) before social isolation for 15 minutes as described above. The duration of vocalisation on drug treatment days is expressed as a percentage of the pre-treatment baseline value for each animal. The same subjects are retested once weekly for up

to 6 weeks. Between 6 and 8 animals receive each test compound at each dose tested.

As used herein, the term "CNS-penetrant" refers to NK-1 receptor antagonists which are able to inhibit NK-1 receptor antagonist-induced foot-tapping in the gerbil as hereinafter defined.

Essentially, hind foot-tapping in the gerbil induced by infusion of the NK-1 receptor agonist, GR73632 (d Ala[L-Pro^9,Me-Leu^{10}]-substance P-(7-11)), under anaesthesia, directly into the central ventricles is inhibited when a CNS-penetrant NK-1 receptor antagonist is administered intravenously immediately prior to GR73632 challenge, wherein hind foot-tapping over a period of five minutes following recovery from the anaesthesia is inhibited with an $ID_{50} \leq 3mg/kg$, and preferably with an $ID_{50} \leq 1mg/kg$.

In an alternative method, the NK-1 receptor antagonist is administered orally, 1 hour prior to GR73632 challenge, wherein the foot-tapping over a period of five minutes following recovery from anaesthesia is inhibited with an $ID_{50} \leq 30mg/kg$, and preferably with an $ID_{50} \leq 10mg/kg$.

CNS-penetrant NK-1 receptor antagonists of use in the present invention are also effective in the attenuation of separation-induced vocalisations by guinea-pig pups as hereinafter defined.

Essentially, a vocalisation response in guinea-pig pups is induced by isolation from their mothers and littermates, which response is attenuated when a CNS-penetrant NK-1 receptor antagonist is administered subcutaneously 30 minutes prior to isolation, wherein vocalisations during the first 15 minutes of isolation are attenuated with an $ID_{50} \leq 20mg/kg$, preferably with an $ID_{50} \leq 10mg/kg$, and especially with an $ID_{50} \leq 5mg/kg$.

In an alternative method, the NK-1 receptor antagonist is administered orally, 4 hours prior to isolation, wherein vocalisations during the first 15 minutes of isolation are attenuated with an

$ID_{50} \leq 20mg/kg$, preferably with an $ID_{50} \leq 10mg/kg$, and especially with an $ID_{50} \leq 5mg/kg$.

A suitable selection cascade for NK_1 antagonists of use according to the present invention is as follows:

(i) Determine affinity for human NK_1 receptor in radioligand binding studies (Assay 1); select compounds with $IC_{50} \leq 10nM$, preferably $IC_{50} \leq 2nM$, especially $IC_{50} \leq 1nM$.

(ii) Determine ability of compounds to penetrate CNS by their ability to inhibit foot tapping in gerbils induced by central injection of an NK_1 agonist (Assay 2); select compounds that inhibit foot tapping with $ID_{50} \leq 3mg/kg$ i.v., and preferably $ID_{50} \leq 1mg/kg$ i.v. when administered immediately prior to central NK_1 agonist challenge, or $ID_{50} \leq 30mg/kg$ p.o., and preferably $ID_{50} \leq 10mg/kg$ p.o. 1 hour prior to challenge.

(iii) Determine central duration of action of compounds in gerbil foot tapping assay following intravenous administration 24 hours prior to central NK_1 agonist challenge; select compounds showing $\leq$ 25-fold loss of potency compared with ID_{50} determined in step (ii) above with the proviso that $ID_{50} \leq 10mg/kg$ i.v., and preferably $\leq 5mg/kg$ i.v. after 24 hour pre-treatment.

(iv) Determine oral bioavailability of compounds by pharmacokinetic analysis, activity in gerbil foot tapping assay following oral administration and/or by ability to inhibit cisplatin-induced emesis in ferrets (Assay 3); select compounds with $ID_{90} \leq 3mg/kg$ p.o., and preferably $ID_{90} \leq 1mg/kg$ p.o.

Particularly preferred compounds of use in the present invention are identified using steps (i) to (iv) followed by step (v):

(v) Determine activity of compounds in assays sensitive to conventional antidepressant/anxiolytic drugs (inhibition of pharmacologically evoked foot tapping in gerbils and/or inhibition of distress vocalisations in guinea-pig pups (Assay 4)). Select compounds with $ID_{50} \leq 20mg/kg$, and preferably $ID_{50} \leq 10mg/kg$.

Yet further preferred compounds of use in the present invention may be selected from those compounds which satisfy the NK-1 receptor binding criteria of step (i) which, in addition, have ≤ 5-fold shift in affinity when incubated in the presence of human serum albumin (HSA) to show non-specific protein binding.

The NK-1 receptor antagonist of use in the present invention is the compound 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, the preparation of which is described in International Patent Specification No. WO 95/18124 and US Patent No. 5,612,337. In the aforementioned assays, this compound has the following activity:

human NK-1 receptor binding:	IC_{50} = 0.12 nM
gerbil foot-tapping (5 mins.):	ID_{50} = 0.38 mg/kg i.v.
gerbil foot-tapping (24 hrs.):	ID_{50} = 2.2 mg/kg i.v.
ferret emesis:	ID_{90} = 1 mg/kg p.o.
guinea-pig vocalisation (4 hr. pre-treatment):	ID_{50} = 0.91 mg/kg p.o.

The following example illustrates pharmaceutical compositions according to the invention.

EXAMPLE 1 Tablets containing 50-300mg of NK-1 antagonist

	Amount mg		
NK-1 antagonist	50.0	100.0	300.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	189.5	139.5	139.5
Magnesium Stearate	0.5	0.5	0.5

The active ingredient, cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 50mg, 100mg and 300mg of the NK-1 receptor antagonist per tablet.

CLAIMS

1. Use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament adapted for oral administration for the treatment or prevention of cognitive disorders.

2. Use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament adapted for oral administration for the treatment or prevention of cognitive disorders in a patient who is non-responsive to heterocyclic antidepressants, SSRIs, serotonin agonists or antagonists, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants, SSRIs, serotonin agonists or antagonists, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated.

3. Use of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament adapted for oral administration for the treatment or prevention of cognitive disorders in a patient who is non-responsive to antipsychotic agents, or for whom antipsychotic agents are contraindicated.

4. An oral pharmaceutical composition for the treatment of cognitive disorders which comprises 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-

(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

5. A method for the treatment or prevention of cognitive disorders, which method comprises the oral administration to a patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

6. A method for the treatment or prevention of cognitive disorders in a patient who is non-responsive to heterocyclic antidepressants, SSRIs, serotonin agents or antagonists, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants, SSRIs, serotonin agents or antagonists, mixed serotonin and norepinephrine selective reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

7. A method for the treatment or prevention of cognitive disorders in a patient who is non-responsive to antipsychotic agents, or for whom antipsychotic agents are contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine, or a pharmaceutically acceptable salt thereof.

8. A use according to claim 1, 2 or 3, or a composition according to claim 4 or a method according to claim 5, 6 or 7 wherein the cognitive disorders are selected from dementia, amnestic disorders and cognitive disorders not otherwise specified.

9. A use, composition or method according to claim 10 wherein the dementia is caused by degenerative disorders; lesions, trauma, infections, vascular disorders, toxins, anoxia, vitamin deficiency or endocrine disorders.

10. A use, composition or method according to claim 8 wherein the amnestic disorders are caused by: alcohol and other causes of thiamine deficiency; bilateral temporal lobe damage due to herpes simplex encephalitis and other limbic encephalitis, neuronal loss secondary to anoxia/hypoglycaemia/severe convulsions, and surgery; degenerative disorders; vascular disorders; or pathology around ventricle III.

11. A use according to claim 1, 2 or 3, or a composition according to claim 4 or a method according to claim 5, 6 or 7 wherein the cognitive disorders are due to cognitive impairment resulting from other medical conditions.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practical search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	WO 99 07375 A (MERCK SHARP & DOHME ;RUPNIAK NADIA MELANIE (GB)) 18 February 1999 (1999-02-18) claims ---	1-11
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[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
28 July 1999	04/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040 Tx 31 651 epo nl, Fax (+31-70) 340-3016	Seegert, K

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